IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	**Rosenblum *et al.***	**ART UNIT:** **1642**
FILED:	**January 7, 1999**	
SERIAL NO.:	**09/226,895**	**EXAMINER:** **Canella, K.**
FOR:	**Potentiation of Anti-CD38-Immunotoxin Cytotoxicity**	**DOCKET:** **D6205**

The Assistant Commissioner of Patents and Trademarks
BOX AF
Washington, DC 20231

ATTENTION: Board of Patent Appeals and Interferences

CERTIFICATE OF MAILING UNDER 37 CFR 1.8

Dear Sir:

I hereby certify under 37 CFR 1.8 that the following correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to Commissioner of Patents and Trademarks, Washington DC 20231.

1) Transmittal letter for Appeal Brief;
2) Three copies of the Appeal Brief (12 pages) and two appendices;
3) Return Post Card.

Please return the enclosed postcard acknowledging receipt of this correspondence.

Respectfully submitted,

Date: Dec 21, 2001

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: Rosenblum *et al.*	§	**ART UNIT:** 1642
FILED: January 7, 1999	§	
SERIAL NO.: 09/226,895	§	**EXAMINER:** Canella, K.
FOR: Potentiation of Anti-CD38-Immunotoxin Cytotoxicity	§	**DOCKET:** D6205

The Honorable Commissioner of Patents
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Washington, DC 20231

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TRANSMITTAL OF APPEAL BRIEF

Dear Sir:

Enclosed please find three originals of the Appeal Brief for the above-referenced patent application.

This application was submitted on behalf of a small entity. Please charge $160 to debit Account No. 07-1185 to cover the fee required for the Appeal Brief. The Commissioner is hereby authorized to debit or credit Account No. 07-1185 if any additional fees are required or any overpayment has been made.

Respectfully submitted,

Date: Dec 21, 2001

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APPELLANT'S BRIEF

This Brief is in furtherance of the Notice of Appeal filed in this case on November 21, 2001. The fees required under 37 C.F.R. §1.17(f) and any other required fees are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF.

In accordance with 37 C.F.R. §1.192(a), this Brief is submitted in triplicate.

INDEX OF SUBJECT MATTER

I. REAL PARTY IN INTEREST

The real party in interest is the Research and Development Foundation.

II. STATUS OF THE CLAIMS

Originally, claims 1-11 were filed with this application. Claims 2, 3, 4 and 10 were cancelled. Pending claims 1, 5-9 and 11 are being appealed; of which, claim 1 is an independent claim.

III. STATUS OF AMENDMENTS

Claims 1 and 5 were amended in response to the Office Action mailed March 2, 2000. Claim 1 is an independent claim.

IV. STATEMENT OF RELATED APPEALS AND INTERFERENCES

To Appellant's knowledge, there are no pending related appeals or interferences that will directly affect or be directly affected by the present appeal.

V. SUMMARY OF THE INVENTION

The claimed methods of the present invention illustrate the potential of retinoid-induced CD38 expression to serve as a target for delivering the immunotoxin anti-CD38-gelonin. The results demonstrate that retinoic acid treatment of leukemia cells, even at very low concentrations (subnanomolar) makes these cells exquisitely sensitive to immunotoxin-induced killing.

The current invention comprises a method of treating an individual having a pathophysiological state, comprising the step of administering to the individual a pharmacologically effective dose of an agent which upregulates the expression of a cellular target and also administering a pharmacologically effective dose of an immunotoxin directed against the upregulated cellular target. The

current invention also comprises a method of treating an individual having a pathophysiological state responsive to retinoid treatment, comprising the step of administering to the individual a pharmacologically effective dose of a retinoic acid metabolite and a pharmacologically effective dose of an immunotoxin.

VI. ISSUES

A. 35 U.S.C. §103(a)

(1) Whether claims 1, 5-9 and 11 are deemed obvious under 35 U.S.C. §103(a).

VII. GROUPING OF CLAIMS

The rejected claims will stand or fall together.

VIII. ARGUMENTS

A. 35 U.S.C. 103(a)

In the Office Action mailed May 22, 2001, claims 1, 5-9 and 11 stood rejected as obvious under 35 USC §103(a) over **Mehta**

et al. (*Proceeding of the American Association for Cancer Research*, 38:88, 1997) in view of **Flavell** *et al.* (*Cancer Research*, 57:4824-4829, 1997), in further view of **Mehta** *et al.* (*Proceeding of the American Association for Cancer Research*, 35:92, 1994). This rejection was maintained in the Advisory Action of November 23, 2001. This rejection is respectfully traversed.

The Examiner argued that even though the anti-CD38-saporin immunotoxin treatment of **Flavell** *et al.* was relatively ineffective, **Mehta** *et al.* overcomes the deficiencies of **Flavell** *et al.* by providing a means to upregulation of CD38 antigen expression so that the anti-CD38-saporin immunotoxin would be effective alone.

Flavell teaches an anti-CD38-saporin immunotoxin but does not teach any methods of enhancing the expression of the target molecule on the surface of a tumor cell. **Mehta** teaches that retinoids stimulate upregulation of CD38 antigen expression and suggests retinoid stimulation of CD38 antigen expression may have clinical utility in the treatment of certain leukemias but provides no specific means for accomplishing this. **Mehta** certainly did not provide additional teachings to suggest the combination of retinoic acid and a single anti-CD38 immunotoxin would be an effective treatment against leukemia or lymphoma. There is no suggestion in

of **Flavell** *et al.* or **Mehta** to combine the teachings of each reference.

The Examiner argued that a person having ordinary skill in this art would be motivated to combine **Flavell** and **Mehta** in order to overcome the deficiency of **Flavell** with respect to lack of a CD38 target on every leukemia cell. The Examiner argued that since **Flavell** demonstrated some effectiveness of an anti-CD38 immunotoxin, one of ordinary skill in the art would expect greater effectiveness against leukemia cells treated with retinoids in a patient, such cells now expressing more CD38 antigens.

The claimed invention must be viewed as a whole. The salient point of **Flavell** was that the anti-CD38 immunotoxin must be administered with two other immunotoxins to be fully effective, not the observation that administrations of a sole anti-CD38 immunotoxin also prolonged the life of experimental animals carrying B-cell lymphoma cells.

The fact that **Flavell** emphasizes the simultaneous use of immunotoxins against multiple cellular markers clearly illustrates that this reference teaches away from the instant invention. A reference teaches away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path

set out in the reference. As **Flavell** stressed the targeting of multiple markers using a triple combination of anti-CD immunotoxins, one of ordinary skill, after a clear reading of **Flavell**, would not resort back to the use of a single immunotoxin, with or without retinoid boosted antigenic expression.

Furthermore, without actually attempting the combination in a manner analogous to that of Appellants' invention, a person having ordinary skill in this art would not be able to determine that the retinoid stimulation of CD38 expression would enable **Flavell's** immunotoxin to be used as the sole administered immunotoxin, without undue experimentation. In addition, a person having ordinary skill in this art would not be able to determine whether the immunotoxin would have remained ineffective against leukemia cells.

The instant invention alleviated the problem in traditional cancer therapy using immunotoxins by the upward regulation of CD antigens on the surface of cancer cells so that more of these cells were now susceptible to anti-CD immunotoxins.

The **Mehta** articles were published in 1994 and 1997 respectively, and **Flavell** was published in 1997. Between 1997 and January 9, 1999, when the instant application was filed, no one of

ordinary skill in the art was motivated to combine **Mehta** and **Flavell** like the Examiner suggested, thus indicating the non-obvious nature of the claimed invention.

As seen in the foregoing paragraphs, Appellants submit that the Examiner has the burden of proving a *prima facie* case of obviousness by a preponderance of the evidence. Appellants assert that this burden has not been met by the Examiner. Therefore, Appellants respectfully request that the decision of the Examiner be reversed, and that claims 1, 5-9 and 11 be allowed.

Respectfully submitted,

Date: Dec 21, 2001

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CLAIMS ON APPEAL

1. A method of treating an individual having a pathophysiological state selected from the group consisting of acute myeloid leukemia, acute promyelocytic leukemia, lymphomas, and myelomas, comprising the steps of:

a). administering to said individual a pharmacologically effective dose of a retinoid which up-regulates the expression of CD38 antigen; and,

b). administering to the same individual a pharmacologically effective dose of an immunotoxin directed against the up-regulated CD38 antigen.

5. The method of claim 1, wherein said retinoid is a material selected from the group consisting of all-*trans*-retinoic acid (RA); 9-*cis* retinoic acid (9-cis RA);(*E*)-4-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-nephthalenyl)-1-propenyl]benzoic acid (TTNPB); and, (*E*)-4-[2-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-nephthalenyl)-1-propenyl]benzoic acid (3-met TTNPB).

6. The method of claim 5, wherein said retinoid is administered in a dose of from about 0.1 mg/kg to about 2 mg/kg.

7. The method of claim 1, wherein said immunotoxin specifically targets cells expressing the CD38 antigen.

8. The method of claim 7, wherein said immunotoxin comprises a monoclonal antibody directed against the CD38 antigen conjugated to a toxin molecule.

9. The method of claim 8, wherein said toxin is gelonin.

11. The method of claim 1, wherein said immunotoxin is administered in a dose of from about 0.05 mg/kg to about 2 mg/kg.